SPECTRUM OF THE GENETIC DEFECTS IN HYPOPHOSPHATEMIC RICKETS IN A GROUP OF TURKISH CHILDREN

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Background and Aim

Hypophosphatemic rickets is characterized by renal phosphate wasting due to various genetic and acquired diseases. There exists limited data regarding genetic etiology of hypophosphatemic rickets in Turkey.

Aim of this study is to investigate the type of genetic defect in 16 index children and their families (12 unrelated, 1 related).

Methods

Following clinical and laboratory assessment, *PHEX* analysis was made initially unless a mutation in another gene was suspected.

If negative, *FGF23, SLC34A3, SLC34A1, CYP27B1, VDR, DMP1, ENPP1* genes were analyzed sequentially.

Results

We identified 21 patients (16 children, 5 adults) with hypophosphatemic rickets. Seventeen of them (80.9 %) had findings related with rickets and 12 (57.1 %) had short stature. Calcium levels were normal, phosphorus low, ALP markedly elevated, and parathormone normal or mildly elevated in all patients.

We found 10 different *PHEX* mutations in 17 patients (80.9%), one novel *SLC34A3* mutation (compound heterozygous mutation; **c.1335+2T>A and c.1639-1652del14**) in two siblings (9.5%), and no mutation in 2 patients (9.5%).

Five *PHEX* mutations were de novo. Four novel *PHEX* mutations were: **c.978_982dupCTACC** (frameshift), **c.1586+2T>G** (splice site), **c.436+1G>T** (splice site), and **c.1217G>T (p.C406F).** Affected parents were all symptomatic but none were diagnosed previously.

Table 1. Clinic and laboratory findings of patients with hypohosphatemic rickets regarding mutation type

	PHEX (n=17)		SLC34A3 (n=2)	No mutation (n=2)
	Adults (n=5) Median (minimum-maximum)	Children (n=12) Median (minimum-maximum)	Median (minimum- maximum)	Median (minimum-maximum)
Age (year)	36 (30-40)	3.3 (1.3-5.0)	6.9 (5.0-8.9)	5.0 (2.5-7.5)
Short Stature (%)	4 (80 %)	8 (66.6 %)	0 (0 %)	0 (0 %)
Osteomalacia/Rickets (%)	4 (80 %)	11 (91.7 %)	0 (0 %)	2 (100 %)
Affected parents (%)	-	5 (41.7 %)	0 (0 %)	0 (0 %)
Height SDS	-3.28[-3.95- (-1.46)]	-2,46 (-3.89-1.18)	-0.39-[-0.54-(-0.23)]	-0.58 [-0.75-(-0.40]
Calcium (mg/dL)	9.7 (9.5-10.1)	9,7 (8.5-10.3)	10.1 (9.8-10.3)	10.1 (9.9-10.3)
Phosphate (mg/dL)	2.1(1.7-2.1)	2,7 (2.0-3.6)	2.56 (2.5-2.6)	2.6 (2.1-3.2)
ALP (IU/L)	111(81-143)	590 (401-925)	436 (325-548)	1483 (434-2533)
25-hydroxy-vitamin D (ng/mL)	15.7(10.5-23.7)	33.7 (4.9-80)	20.0 (12.5-27.5)	6.8 (6.8-6,8)
PTH (ng/mL)	67.1(40-130)	71,5 (31.9-154.7)	27.5 (13.0-33.9)	37.5 (16.9-58.00)
Urine calcium/creatinine ratio	0.05(0.04-0.18)	0.04 (0.01-0.15)	0.31 (0.23-0.38)	0.01 (0.01-0.01)
TPR	87(69.9-95.5)	69.1 (56.9-79.6)	83.8 (82.5-85.0)	76 (70-82)
TmP/GFR	1.69(1.46-1.70)	1.90 (1.31-2.48)	2.5 (2.1-3.0)	1.42 (1.1-1.74)

SDS: standart deviation score, ALP: alkaline phosphatase, PTH: parathormone, TPR: tubular phosphate reabsorption, TmP/GFR: tubular maximum reabsorption rate of phosphate to glomerular filtration rate.

Conclusion

- Present study confirmed that PHEX mutation seems to be the most prevalent mutation in Turkey as well.
- Some cases with hypophosphatemic rickets appear to result from yet uncovered genetic alterations.
- More attention should be paid to hypophosphatemia by the clinicians since some cases remain undiagnosed both during childhood and adulthood.

References

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